

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Attorney Docket No.: DEX-0172
Inventors: Salceda et al.
Serial No.: 09/763,978
Filing Date: April 25, 2001
Examiner: Aeder, Sean E.
Customer No.: 32800
Group Art Unit: 1642
Confirmation No.: 3638
Title: A Novel Method of Diagnosing,
Monitoring, Staging, Imaging and
Treating Various Cancers

Declaration by Patrick M. Sluss, Ph.D.

I, Patrick M. Sluss, Ph.D. hereby declare:

1. I was awarded a Bachelor of Arts [Zoology] in 1970 by the University of California, Berkeley, CA, a Master of Arts [Zoology] in 1973 by the University of California, Davis, CA, and a PhD [Physiology and Biophysics] in 1981 by Colorado State University, Ft Collins, CO. After obtaining these degrees I served a two year post-doctoral traineeship in Biochemistry at Albany Medical College, Albany NY.

2. I am presently Associate Director of the Pathology CORE Laboratories at Massachusetts General Hospital in Boston, MA. My current academic positions are as Assistant Professor in both Medicine and Pathology at the Harvard Medical School. I am also the Director of the Reproductive Endocrine Reference Laboratory and the Boston Area Diabetes Endocrine Research Center's Immunoassay Core laboratory. The laboratories that I oversee perform clinical testing services for patient care, human investigations and animal research. My basic investigations involve the biochemistry, physiology and pathophysiology of the activin-binding protein follistatin. Recent studies have focused upon

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identifying the specific epitopes directly involved with activin binding and delineating allosteric effects of activin binding in altering domain-specific antigenic epitopes in the holoprotein. In addition, my laboratory is involved in clinical studies directed toward developing methods and technological approaches for serum measurements of novel ovarian cancer markers using SELDI and other high resolution proteomic procedures. My laboratory also conducts studies of commercially available and new immunodiagnostic assays to evaluate their analytical performance and clinical utility. These studies encompass immunoassays for endocrine hormones, tumor markers, cardiac markers, and therapeutic drugs.

3. Having worked in the area of immunodiagnostics for over 20 years, I am very familiar with the methods and tools used to identify antibodies for a protein or peptide encoded by a defined nucleic acid.

4. I have reviewed the above-referenced patent application and the Office Action mailed October 22, 2007. In particular, I have reviewed the Examiner's reasoning behind his statement that "the specification does not teach the protein sequence or the open reading frame of SEQ ID NO:1" and "[t]hus . . . does not provide enough information to indicate for which protein the claimed antibodies are specific". I disagree that utility of antibodies for a diagnostic cancer marker expressed by a defined nucleic acid is dependent upon identification of "the" protein sequence or the open reading frame.

5. The Sequence Listing of the patent application sets forth a number of nucleic acid sequences including SEQ ID NO:1 and associated fragments, e.g. SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12 and SEQ ID NO:13. A number of characteristics of SEQ ID NO:1 are described in the patent application and/or are ascertainable from the nucleic acid sequence itself. Perhaps of most importance is data presented in Examples 1 and 2 of the patent application relating to mRNA overexpression of Ovr110. This data demonstrates to me the utility of Ovr110 as a diagnostic marker for gynecologic cancers.

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6. Generating proteins and peptides encoded by a nucleic acid was routine as of 1998, and there were a number of computer programs routinely used as of 1998 to identify potential open reading frames and deduced proteins and peptides expressed by a defined nucleic acid sequence.

7. Also routine as of 1998 was to utilize the generated proteins and peptides encoded by the defined nucleic acid sequence (such as SEQ ID NO:1 or its fragments) to make antibodies and to routinely select antibodies for their ability to detect cancer.

As discussed below, once the nucleic acid sequence is specified there were several approaches available to those skilled in the art in 1998 to generate antibodies that could be used to formulate tests for circulating proteins originating from the nucleic acid sequence revealed. It is the teaching of the patent that this sequence, and the other sequences revealed by the "ovary specific gene" approaches described, is associated with ovarian cancer that focuses the well established routine work needed to then generate and validate antibody-based diagnostic methods that utilize the coded proteins as biomarkers for ovarian cancer.

8. Further, I disagree with the Examiner's suggestion that identification of a protein sequence or an ORF in the patent application is required for one of skill to identify structural or functional attributes of antibodies to proteins or peptide fragments of a defined nucleic acid sequence.

The nucleic acid sequences contain all the information needed for one skilled in the art to predict, using software tools available in 1998, all proteins that could be coded. These protein sequences could then be used in homology searches, again using software and databases available at the time, to identify target immunogens for specific antibody generation.

The predicted sequences could also have been subjected to antigenic epitope modeling to identify small immunogens that could easily be synthesized and use to generate panels of site specific monoclonal antibodies which then could be

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routinely selected for recognition of endogenous protein products of the nucleotide sequences taught in the patent.

9. Thus, I believe this patent application does provide sufficient information to identify antibodies or antibody fragments that bind to and/or detect proteins or protein fragments expressed by SEQ ID NO:1 which are useful as cancer diagnostic agents.

I hereby declare that all statements herein of my own knowledge are true and that all statements made on information or belief are believed to be true; and further that these statements were made with the knowledge that willful statements and the like so made are punishable by fine or by imprisonment, or both, under §1001 of Title 18 of the United States Code, and that such willful statements may jeopardize the validity of the application, any patent issuing there upon, or any patent to which this verified statement is directed.



Patrick M. Sluss

4/21/2008

Date